the functional relationships among Asf1, other chaperones, and chromatin modifiers? The candid picture of the H3/H4 couple sitting in the Asf1 loveseat represents a milestone in our understanding of how chromatin is assembled.

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Worms Clear the Smoke Surrounding Nicotine Addiction

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In this issue of *Cell*, Feng et al. (2006) report a worm model of nicotine dependence that shows behavioral adaptations surprisingly similar to those in humans. These authors show a critical link between nicotinic receptors and TRP channels, which may represent a new therapeutic target for treating nicotine addiction.

There is often striking phylogenetic conservation of function within the rich array of chemical signaling molecules in the brain. In the lobster, the neurotransmitter serotonin regulates dominance behavior, and in humans, serotonin is thought to be a key modulator of mood, impulse, and aggression. Dopamine receptors are important in reward learning in honeybees, molluscs, mice, and primates. An additional feature of neurochemical evolution is that many of these shared substrates also serve as targets for drugs of abuse, some of which are plant alkaloids that coevolved with animals. In this issue, Feng and colleagues (2006) report nicotine-dependent behavior in the nematode *Caenorhabditis elegans*, which mimics that observed in mammals, including humans (Feng et al., 2006). Through elegant experiments, the authors pinpoint the genetic and biochemical mechanisms underlying this behavior in worms and discover that TRP (transient receptor potential) channels modulate the activity of nicotinic acetylcholine receptors (nAChRs). As nicotine addiction is a major cause of morbidly and mortality worldwide (Laviolette and van der Kooy, 2004), a simple animal model of nicotine addiction may reveal new therapeutic targets for treating this health problem.

Nicotine, the component in tobacco smoke that leads to addiction, acts on nAChRs in the brain. These receptors, which are ligand-gated ion channels, are widely distributed in the central and peripheral nervous system in nearly all invertebrate and vertebrate species. These receptors consist of a variety of pentameric combinations of α and β subunits that form cation-selective pores (Dani and Bertrand, 2006). Receptors composed of $\alpha7$ and $\alpha4\beta2$ subunits have received particular attention with regard to the cognitive and reinforcing effects of nicotine. Indeed, in rodents, the $\beta2$ subunit is a critical player for releasing dopamine in response to nicotine and for reinforcing nicotine's effects (Maskos et al., 2005; Picciotto et al., 1998). Nicotine also has potent effects on glutamatergic transmission in brain regions important for learning, memory, and attention in rodents (Gray et al., 1996). In the mammalian brain, the widespread distribu-

tion of nicotinic receptors in cortical and limbic regions suggests that they may have a fundamental role in cognition and memory.

Feng et al. (2006) first established that the effects of nicotine on behavior in *C. elegans* share common properties with mammalian models of nicotine addiction. Using an assay that measures locomotion velocity, they show that acute exposure of worms to nicotine causes a clear dose-dependent increase in locomotion. Chronic nicotine exposure results in tolerance, as the dose that normally elicits locomotion was no longer capable of doing so. Notably, the animals also showed signs of withdrawal: When nicotine was removed from the medium of chronically exposed worms, the animals displayed an abnormal increase in locomotor behavior. The worms also displayed sensitization, showing an enhanced locomotor response to a low nicotine dose when intermittently exposed. These phenomena—psychomotor stimulation, tolerance, withdrawal, and sensitization—have been linked to addictive processes in humans (Laviolette and van der Kooy, 2004). Such parallels in the worm are quite striking.

Next, the authors systematically examined the genetic and neural mechanisms underlying this profile of behavior. After showing that a selective nicotinic antagonist blocked the acute response and elicited withdrawal in dependent animals, a screen for nAChR mutants indicated that two (*acr-15* and *acr-16*) lacked a response to this treatment. Remarkably, behavior associated with nicotine could be rescued in these worm mutants by expressing a mouse transgene encoding $\alpha4\beta2$ (the $\alpha7$ transgene did not afford rescue). This important observation suggests that genes regulating the activating and reinforcing effects of nicotine are functionally conserved between worms and mammals.

To demonstrate neural specificity, the authors showed that expression of the *acr-15* gene in command interneurons (important for locomotor behavior) rescues the worm mutant phenotype and that selective destruction of these neurons results in a loss of the nicotine response in wild-type worms. Then, using calcium imaging in live animals, they demonstrated that acute nicotine exposure induced a robust calcium ion response in the command interneurons. This response was enhanced by sensitization and was not observed in animals chronically exposed to nicotine. Importantly, no calcium ion response was observed in the *acr-15* mutant worms.

In perhaps the most interesting aspect of the study, the authors investigated the role of TRP channels in nicotine-induced behavior in worms. TRP channels are part of a superfamily of related cation channels that are critical modulators of calcium ion entry into cells (Montell et al., 2002). The authors speculated that one of these channels, TRPC (TRP canonical), might be a key molecule in the nicotine responses observed in *C. elegans*. In confirmation of this notion, the authors observed that worms with a mutation in either *trp-1* or *trp-2* (the worm homologs of TRPC) exhibit no response to acute nicotine exposure. However, transgenic expression of the *trp-2* gene on a *trp-2* mutant background restored the acute response to nicotine as well as withdrawal and sensitization responses. Indeed, expression of TRP-2 rescued not only the *trp-2* worm mutant phenotype but also that of the *acr-15* mutant. As both TRP-2 and ACR-15 are expressed in the worm's command interneurons, these results suggest that these two proteins could interact in neurons that control nicotine-associated behavior.

In a final series of studies, the authors formulate a general mechanism by piecing together several known characteristics of TRP channels and how they may relate to the events following stimulation of nAChRs. TRP channels can be activated by stimulation of phospholipase Cβ (PLCβ). Carbachol, which stimulates nAChRs, does so by inducing calcium ion entry via stimulation of PLCβ. When the authors expressed the *trp-2* gene in a HEK293 cell line, carbachol treatment resulted in calcium ion entry into the cells, an effect that was blocked by a PLCβ antagonist. The authors then showed that nicotine-induced calcium ion entry in command interneurons was reduced in *trp-1* and *trp-2* mutant worms. These experiments suggested to the authors that nicotine produces its behavioral effects in the worm by stimulating (via a membrane-bound nAChR) phospholipase-dependent activation of TRP channels, which promotes calcium ion entry and activates neurons responsible for locomotor function.

This work is an impressive example of the use of an invertebrate model to tease apart precise cellular mechanisms underlying drug effects that are relevant to mammals. It represents a highly integrative approach, including sophisticated behavioral measurements, genetic manipulations, pharmacology, and cellular imaging. The data are an important addition to a growing literature demonstrating shared behavioral characteristics of psychoactive drugs between invertebrates and vertebrates. Indeed, the authors show that expression of a human TRP-channel transgene restored the nicotine response in *trp-2* mutant worms. In the fruit fly *Drosophila*, cocaine, nicotine, and ethanol induce behavioral responses that are dependent on dopamine, as is the case in mammals (Bainton et al., 2000). The phenomena of sensitization and tolerance have been demonstrated in flies for ethanol and cocaine (McClung and Hirsh, 1998; Scholz et al., 2000). Invertebrates prefer an environment associated with drug exposure—for example, crayfish show a place preference for stimuli associated with cocaine and amphetamines (Panksepp and Huber, 2004). Thus, the ability of addictive drugs to induce neuroplastic and rewarding effects is phylogenetically conserved.

Taken together, these studies provide a framework for thinking about the evolution of psychoactive drug use in human cultures. Clearly, genes for neurotransmitter (and drug) receptors evolved hundreds of millions of years ago, in an environment rich in plant alkaloids. Some of these alkaloids perhaps served as toxic defense

mechanisms against animal predators. The structure of many of these alkaloids bears a close resemblance to vertebrate and invertebrate neurotransmitters—for example, ergots to serotonin, opiates to opioid peptides, cannabinoids to endocannabinoids, and cocaine to catecholamines. This coevolutionary relationship between plants and humans may have been beneficial in our ancestral environment. For example, use of plants such as tobacco and coca may have provided alternative energy sources when food was scarce (Sullivan and Hagen, 2002). However, the present cultural environment provides nearly unlimited sources of substances (including food) that stimulate these endogenous chemical systems, sometimes resulting in maladaptive compulsive use. Further work should be directed at questions that are unanswered by Feng et al.'s data, such as how and where the TRPC-channel protein interacts with nicotinic receptors and whether the relationship holds true for other species and other drug responses. Studies of this nature in simple animal models may reveal new avenues for understanding addiction and its treatment in humans.

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The HeArt of Regeneration

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Fish and amphibian hearts are known to regenerate after partial resection, but the molecular mechanisms underlying this process remain unclear. In this issue of *Cell*, Lepilina et al. (2006) analyze regeneration in the zebrafish heart. Their work indicates that new cardiomyocytes originate from undifferentiated progenitor cells and reveals a critical role for the epicardium, the cellular layer that covers the heart.

Injury to the myocardium is a major cause of death, as the human heart has a limited capacity to regenerate. Possible approaches to treat heart failure include (1) transplantation of bone marrow or other progenitor cells into the heart and (2) boosting regeneration through inducing endogenous cells to differentiate/proliferate in situ to replace lost cardiomyocytes. Recent clinical trials injecting bone marrow into the injured heart have yielded mixed results (reviewed by Rosenzweig, 2006). Manipulating the regeneration potential of the adult heart may be the best strategy, but it is also the most challenging.

Adult zebrafish, in contrast to mammals, are able to fully regenerate cardiac muscle (Poss et al., 2002). Following surgical removal of the apex of the ventricle—approximately 20% of the ventricle's volume—the missing tissue is fully regenerated within 2 months. As a result, the zebrafish has become a favorite model for studying cardiac regeneration, as this vertebrate system combines substantial regenerative capacity with the ability to carry out genetic analyses. Elucidating the mechanisms underlying regeneration should enable us to better understand why the mammalian heart exhibits very limited regenerative capacity despite the presence of cardiac progenitor cells in mouse, rat, and human postnatal myocardium (reviewed in Srivastava and Ivey, 2006). By investigating which cells